Note that prior to the Office Action dated August 23, 2002, the relevant portions of Claims 1, 12, and 19 read:

> "... each first primer having an overall length of at least about 10 nucleotides..."

Applicant's undersigned counsel had a personal interview with Examiner Sisson, in which the Examiner suggested that an upper limit be added to the length of the primers. In response, Claims 1, 12, and 19 were amended to read, in relevant part:

> "... each first primer having an overall length of **[at least]** **from** about 10 nucleotides **to about 30 nucleotides**..."

Thus, the language of Claims 1, 12, and 19 as they presently stand reads, in relevant part:

> "... each first primer having an overall length of from about 10 nucleotides to about 30 nucleotides..."

Applicant's prior amendment could necessitate the new grounds of rejection only if the new rejection was predicated in some fashion upon the upper limit for the primer length, the only limitation that was added to the claims in Applicant's last response.

The Deugau et al. reference, however, is cited for the first time in the present Action and the Office makes no comment regarding the upper limit to the length of the primers taught in the Deugau et al. reference.

Note also that the lower limit of the length of the primers read "of at least about 10 nucleotides...," in Claims 1, 12, and 19 as they were earlier formulated, and the lower limit on the length of the primers now reads "of from about 10 nucleotides to about 30 nucleotides...." The point being that the language dictating the lower limit of the primers is, in effect, unchanged in either reading of the claims. Therefore the lower-end limit of the

primer length cannot be considered a substantive amendment that could necessitate a new grounds for rejection - the amendment to the lower limit was formal only, not substantive.

Applicant therefore respectfully submits that the finding of finality in the Office Action dated November 25, 2002 is premature. Withdrawal of the finality of the Office Action is respectfully requested.

Rejection of Claims 1-8, 10-12, 14-27, 28, and 29 Under §103(a) in View of Deugau et al., U.S. Patent No. 5,508,169:

This rejection is respectfully traversed because the protocol described in the Deugau et al. reference in no way teaches or suggests performing PCR using:

> (1) a first set of primers that have a region of fixed nucleotide sequence identical or complementary to a consensus sequence of interest and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence; and
>
> (2) a second set of PCR primers that have a region of arbitrary, yet fixed nucleotide sequence and a region of randomized nucleotide sequence located 5' to, 3' to, or flanking the region of fixed nucleotide sequence

Applicant traverses this rejection on the grounds that: (1) the Office is using Applicant's own disclosure to provide a motivation and/or suggestion that is lacking in the Deugau et al. patent; and (2) modifying the Deugau et al. reference to arrive at the presently claimed invention will destroy the functionality of the invention described in the Deugau et al. patent.

The Deugau et al. patent describes a protocol wherein "indexing linkers" are ligated to the cohesive ends of a DNA strand to be amplified. These indexing linkers generally comprise a double-stranded oligonucleotide, having at least one single-stranded overhang. See Deugau et al., col. 6, lines 47-54. The double-stranded portions of the linkers have a fixed, "common" sequence. See Deugau et al., col. 6, lines 28-42. The indexing linkers are then ligated to enzymatically digested DNA, the overhangs of the indexing linkers serving to

provide a means to ligate the indexing linker to the ends of the digested DNA. The digested DNA with the indexing linkers attached can then be amplified using primers that are "linker-specific." See Deugau et al. Figs. 3a, 3b, and col. 11, lines 26-44.

A critical difference, however, exists between the Deugau et al. disclosure and the present invention. The Office states that because Deugua et al. teach that all possible permutations of A, T, C, and G can be used in the protruding, single-stranded termini of the linkers, it would be obvious to use an equally varied set of primers, such that the sequences present in the library would be amplified. **But that is not what is explicitly taught by the Deugau et al. reference itself**. And the only motivation to amplify Deugau's "indexed" DNA using such a primer is provided by Applicant's own disclosure (which cannot be used in this fashion).

Deugau et al. explicitly state the primers used to hybridize to the "indexed" DNA are "complementary" to the indexing linkers. See Deugau et al., col. 11, lines 30-35:

> In the presence of **complementary** primers hybridized to the indexing linker at the 3'-end of each fragment strand, the members of the class, up to the maximum practical size for PCR amplification, may be amplified according to the prior art. (Emphasis added.)

Moreover, note that Deugau et al. explicitly disclose that a primer fixed in sequence from end-to-end was used in **all** of the Examples in the Deugau et al. patent. See the Note at the bottom of Table 1, of Deugau et al., col. 15, lines 55-60:

> The common portion of each linker was complementary to oligonucleotide No. 1026, GGATCCGGATGCGAAGACGG, used to form the double stranded part of the linkers.

In Examples 1-3 of the Deugau patent, this single, fixed oligonucleotide, No. 1026, was used as the PCR primer. See Deugau et al. Example 1: col. 17, line 37 ; Example 2: col. 18, line 33; and Example 3: col. 19, lines 38-41;

Note that in Example 4, additional primers were added to each amplification, but these primers, like No. 1026, were also all fixed from end-to-end and complementary to the fixed, "common" portion of the indexing linker. See Example 4: col. 21, lines 1-8, and the notes to Table II at col. 16, line 15.

Thus, Deugau et al disclose, in no uncertain terms, that the primers used are fixed in sequence from end-to-end and are complementary to the fixed, common portion of the indexing linker. In no instance does Deugau et al. ever teach or even remotely suggest using a primer having a fixed portion and a randomized portion. In every instance described in the Deugau patent, the primer is of fixed sequence and wholly complementary to the "common" portion of the indexing linker.

For this reason, Applicants submit that the Office has failed to present a *prima facie* case of obviousness because the applied referenced, Deugau et al, fails to suggest arriving at the presently claimed invention. Deugau et al. used primers having a fixed sequence. As noted above, any motivation to alter the fixed-sequence primers disclosed by Deugau et al. to arrive at the partially randomized primers required by the present claims requires an improper use of the Applicant's own disclosure. In short, no such motivation or suggestion of a partially randomized primer is provided by the Deugau et al. reference.

On this basis alone, Applicant respectfully submits that this rejection is improper and should be withdrawn.

Applicants also note, for sake of completeness, that the rejection is also improper because there is no technical motivation to make the suggested modification to the Deugau et al. disclosure. The stated goal of the Deugau et al. reference is to amplify the "indexed" DNA's selectively. But each "indexed" DNA includes a sequence that is common to each "index linker." In short, why randomize the primers of Deugau et al. when a single primer that is fully complementary to the "common" portion of the index linkers will amplify all of indexed DNA's?

Randomizing even a portion of the Deugau et al. primers destroys the utility of the protocol described in the Duegau patent because these partially randomized primers would no longer be perfectly complementary to the already-known sequence of the common portion of the index linkers. Thus, the specificity of the resulting amplification would be destroyed, rather than improved.

It is well-settled law that a *prima facie* case of obviousness cannot be shown where the modification suggested by the Office destroys the utility of the invention described in the applied prior art reference. This situation applies here. Deugau et al. explicitly describe using a primer exactly complementary to the common portion of the index linkers. Altering that perfect complementarity destroys the specificity of the primer for its intended target. Therefore, there is no motivation to make the proposed modification in the first instance.

Applicant therefore respectfully submits that this rejection is improper. Withdrawal of the same is now requested.

CONCLUSION

Applicant respectfully submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the U.S. Patent & Trademark Office, via fax, to: 703-872-9307

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Date of Deposit: 25 FEB 2003

Signature: